

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020916

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

REVIEWER : Houda Mahayni, Ph.D.
NDA : 20916
TYPE : 6S
DRUG : Omeprazole (Prilosec®)
FORMULATION : Delayed-release capsule
APPLICANT : Astra Merck Inc.

SUBMISSION DATE: 09-30-97, 01-30-98
DRAFT REVIEW : 02-13-98, 06-01-98, 06-10-98
FINAL REVIEW : 06-19-98
INDICATION : Eradication of *H. pylori*

BACKGROUND/RATIONALE:

PRILOSEC®(omeprazole) (5-methoxy-2-{{(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl} sulfinyl}-1H-benzimidazole) is a highly specific and effective inhibitor of gastric acid secretion. Omeprazole has been approved for marketing in the US since 1989. In addition, omeprazole, in combination with clarithromycin, received US approval (1996) for the short-term treatment of patients with *H. pylori* infection to reduce the risk of duodenal ulcer (DU) recurrence. This application provides for the use of omeprazole in combination with amoxicillin and clarithromycin for the eradication of *H. pylori* infection in patients with duodenal ulcer disease. This application does not provide for a new dosage form nor does it seek a change in the packaging of any of the elements of the regimen. The dosage regimen studied in the present application is omeprazole 20 mg bid in combination with amoxicillin 1000 mg bid and clarithromycin 500 mg bid for 10 days in eradicating *H. pylori* infection in patients with duodenal ulcer disease, and thus, reducing the risk of duodenal ulcer recurrence. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of PRILOSEC 20 mg once daily is recommended for ulcer healing and symptom relief.

OMEPRAZOLE:

PRILOSEC Delayed-Release Capsules contain an _____ formulation of omeprazole (because omeprazole is acid-labile), absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within _____ hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability is about _____ at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects, the plasma half-life is _____ hour and the total body clearance is _____ mL/min. Protein binding is approximately 95%. Following a single oral dose of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic

acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma as the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

AMOXICILLIN:

Amoxicillin is stable in the presence of gastric acid. It is rapidly absorbed after oral administration. The half-life of amoxicillin is 61.3 minutes. Most of the amoxicillin is excreted unchanged in the urine. Amoxicillin is not highly protein-bound. Orally administered doses result in average peak blood levels 1 to 2 hours after administration. Detectable serum levels are observed up to 8 hours after an orally administered dose. Approximately 60% of the dose is excreted in the urine within hours.

CLARITHROMYCIN:

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg clarithromycin tablets was approximately 50%. Food slightly delays both the onset of clarithromycin absorption and the formation of the antimicrobially active metabolite, 14-OH clarithromycin, but does not affect the extent of bioavailability. Peak concentrations were attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations were attained in 2 to 3 days. The elimination half-life of clarithromycin was hours with 500 mg administered every 8 to 12 hours. With a 500 mg every 8 to 12 hours dosing, the peak steady-state concentration of 14-OH clarithromycin is slightly higher, and its elimination half-life is about hours. Its steady-state concentration is attained within 2 to 3 days. At the 500 mg dose every 12 hours, the urinary excretion of clarithromycin is approximately 30%. The renal clearance approximates the normal glomerular filtration rate.

SUMMARY OF STUDIES:

Studies I-1238 and I-1221 indicated that the bioavailability of amoxicillin (AUC and C_{max}) were similar when amoxicillin was given alone or concomitantly with omeprazole. Omeprazole mean AUC when given alone was equivalent to the mean omeprazole AUC when given concomitantly with amoxicillin. Therefore, amoxicillin and omeprazole are similarly bioavailable when administered alone or in combination. Whereas, when omeprazole was given in combination with clarithromycin, the steady state plasma concentrations of omeprazole were increased. Also, the plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. Most of amoxicillin is excreted unchanged in the urine with an elimination half life of 61.3 minutes while clarithromycin is metabolized by the cytochrome P450 system into its antimicrobially active metabolite, 14-hydroxy-clarithromycin. Therefore, based on having independent elimination pathways, it is unlikely that any potential inhibition of amoxicillin metabolism by clarithromycin would have a significant impact on amoxicillin pharmacokinetics, or vice versa. The mean plasma concentrations of omeprazole was higher when omeprazole, amoxicillin, and clarithromycin were administered concomitantly,

This resulted in a two-fold increase in mean AUC and a 68% increase in mean C_{max} . The $t_{1/2}$ of omeprazole was also slightly longer (32%) while the T_{max} did not seem to be altered. Also, the mean plasma concentrations of amoxicillin after triple drug administration seemed to be slightly higher than those obtained after administration of amoxicillin alone. Accordingly, the mean C_{max} and AUC of amoxicillin were % higher. The mean concentrations of clarithromycin and of 14-hydroxylclarithromycin both seemed to be slightly higher during triple drug administration than during administration of clarithromycin alone. The C_{max} and the AUC of 14-hydroxylclarithromycin were approximately 30% higher during triple drug treatment than during single drug administration.

GENERAL COMMENTS:

1. The sponsor submitted studies evaluating the European formulations Losec, Imacillin and Bremon. No information was submitted on the composition and components of these dosage forms and how they differ from those marketed in the US.
2. The sponsor did not submit in-vitro dissolution data to compare the European formulations studied to the US formulation composition.
3. Limited assay validation was submitted.
4. Some flaws were found in the protocol and report of the pivotal study.
5. We had a teleconference with the sponsor on April 1, 1998 to request the submission of a revision for the pivotal study SH-OMH-0016. In addition, we requested quantitative formulation composition and in-vitro dissolution profiles for each drug, and quality control/validation data for all the studies. The sponsor's submission of April 10, 1998 was a response to our telecon. It contained partial amendment of study protocol SH-OMH-0016, partial bioanalytical assay quality control data for study SH-OMH-0016. The analytical validation and quality control data submitted for study I-1221 and I-1214 was only for the determination of one of the drugs studied (amoxicillin).
6. Clarithromycin and omeprazole are approved. To date, there has been no major clinical adverse event from coadministration of 40 mg omeprazole and 500 mg clarithromycin.
7. Literature search revealed no major interaction between amoxicillin and clarithromycin or omeprazole
8. Adverse events from current clinical trials in support of the NDA were mainly diarrhea, headache, taste perversion, flatulence, and respiratory infection.
9. All three drugs have been individually approved in the past. Two drugs (clarithromycin and omeprazole) have been used together for the same indication as sponsor is seeking in this NDA. Therefore, the addition of amoxicillin, the third drug, to this regimen is not expected to produce drastic pharmacokinetics interaction because amoxicillin is eliminated renally, whereas clarithromycin and omeprazole are metabolized by the liver.

LABELING COMMENTS: Because of lack of adequate information on the assay quality control as well as how the formulations studied compare to the US formulations, study SH-OMH-0016 and other studies are not found acceptable. Thus, the results from these studies can not be used in the label.

The following are the labeling comments:

1. Changes to the Clinical Pharmacology section.

Page 107, 2nd paragraph should read:

2. Changes to the Precautions section

Page 117, paragraph 6 should read:

RECOMMENDATION:

The submitted data in the (Human PK and BA section of NDA 20-916) has been reviewed and was not found acceptable (see General Comments). However, the approval of NDA 20-916 is supported based on the clinical use history of these agents (General Comments # 8&9). Please pass the labeling comments to the sponsor.

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6/19/98

Houda Mahayni, Ph.D.
Pharmacokinetics Reviewer, DPEIII
Office of Clinical Pharmacology and Biopharmaceutics

CPB briefing (6-4-98) attendees: John Lazor, Funmi Ajayi, Dennis Bashaw, Carol Cronenberger, Steve Hundley, Robin Anderson

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6/19/98

Concurrence: Funmi Ajayi, Ph.D.
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cc: HFD-590 NDA 20916
/MO/RHopkins
/CSO/RAnderson
HFD-880 /Biopharm/HMahayni
HFD-880 /TLBiopharm/FAjayi
HFD-880 /DPEIII
CDR /Bmurphy

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APPENDIX I
(SUMMARY OF STUDIES)

TITLE: Interaction Between Amoxicillin and Omeprazole During Combination Therapy in Helicobacter Pylori Positive Subjects (Protocol No. I-1238; Vol. 4; pp. 006-001-017 to 006-001-226)

INVESTIGATOR: -----

OBJECTIVES:

1. To investigate the possible pharmacokinetic interaction between amoxicillin and omeprazole when the two drugs were administered simultaneously.
2. To investigate the possible correlation between the bioavailability of amoxicillin and the 24-hour intragastric pH-profiles obtained during omeprazole treatment.

SUBJECTS:

Twenty-four healthy male subjects with Helicobacter pylori infection were to be included. Drop-outs were to be replaced to have 24 subjects completing the study.

STUDY DESIGN:

This was a three-way cross-over double-blind design using double-dummy technique. Amoxicillin and omeprazole were administered alone and in combination. The subjects were randomized to one of 6 possible treatment sequences, with four subjects in each sequence. Each period was separated by a wash-out period of 4 weeks. A 24-hour intragastric pH-metry and a simultaneous determination of serum amoxicillin and omeprazole profiles were performed at steady state in each period. A baseline 24-hour pH-metry was performed at the end of a run-in period on placebo treatment.

FORMULATIONS:

Omeprazole (Losec® Astra AB, Södertälje), capsules (size1) containing 40 mg, as Batch No. H743-2-4-4, dispensed in capsules, were taken orally. Omeprazole-placebo capsules, (size 1), Batch No. H761-2-3-3, were taken orally. Amoxicillin (Imacillin® Astra AB, Södertälje) 750 mg tablets, Batch No. H783-2-2-1, were taken orally. Amoxicillin placebo tablets, Batch No. H784-2-2-1, were taken orally. The omeprazole/placebo capsules and amoxicillin/placebo tablets were packed in appropriately labelled blister packs, one for each subject containing 14 capsules, and 14 tablets each. Omeprazole/placebo capsules as well as amoxicillin/placebo tablets were taken twice daily, once in the morning before breakfast and once in the evening approximately 12 hours after the morning dose of omeprazole, for 5 days.

SAMPLE COLLECTION:

Blood samples (5 mL) for determination of amoxicillin and omeprazole in serum were collected before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 12.25, 12.50, 13, 13.5, 14, 15, 16, 18, 20, 22, 23 hours after administration.

ANALYTICAL METHODS:

***HELICOBACTER PYLORI* STATUS**

The breath samples was analyzed by

The increased amount in ^{13}C in the expired CO_2 was evaluated. A subject was regarded as H.Pylori positive if the increase in ^{13}C was more than 5 pro mil in the ^{13}C -urea breath test.

INTRAGASTRIC PH-METRY

The intragastric pH-metry was performed with a pH sensitive glass electrode

The electrode was calibrated in buffers of pH 7 and 1. The tip of the electrode was positioned in the fundus corpus region approximately 5 cm distal to the cardia. The correct position was controlled by fluoroscopy. Data sampling was done with a solid state data recorder

OMEPRAZOLE AND AMOXICILLIN

The serum samples were analyzed for omeprazole (BA-222) and amoxicillin (BA-225) at Bioanalytical Chemistry at Astra Hässle AB, using a method.

Method is referenced as an article no data was provided on validation or quality control. Article: Lagerström P-O, Persson B-A. Determination of omeprazole and metabolites in plasma and urine by J. Chromatography 1984; 309:347-356.

PHARMACOKINETIC/ DATA ANALYSIS:

The area under plasma concentration(AUC) vs. Time curve for the dosing interval was calculated from zero time to the last detectable sampling point (tn). The AUC was calculated according to the linear trapezoidal method over a 24-hour period (study day) and was expressed as nmol*h/L. C_{\max} and T_{\max} were also assessed. If C_{\max} occurred at more than one measurement, the time to the first measurement with C_{\max} was used.

The analyses of AUC and C_{\max} were performed in an ANOVA model with fixed factors for treatment and period and sequence and a random factor for subjects within sequence. The least squares estimates of the treatment differences between single and combination treatment for omeprazole and amoxicillin with respect to $\log(\text{AUC}_0\text{-tn})$ and $\log(C_{\max})$ were calculated. Confidence intervals with a confidence level of 90% were calculated as the estimates \pm the 0.05 t-quantile multiplied by the standard error of the estimate.

PHARMACODYNAMIC/ DATA ANALYSIS:

The correlation between the pH median and AUC of amoxicillin when administered in combination with omeprazole was estimated using Pearson's product-moment correlation. The hypothesis of zero correlation was tested using Student's t-distributions.

RESULTS:

Of the 36 subjects randomized into the study, 35 entered the run-in period, 6 never took the study drug and thus 29 subjects remained for "All subjects treated" analysis of adverse events. Two subjects violated the study protocol and 27 subjects were included in the "Per protocol" analysis. Subject No. 8 discontinued due to negative UBT-test at visit 6. Subject No. 15 took a drug, which was not allowed according to the protocol, and was therefore excluded from the study.

PHARMACOKINETICS EVALUATION OF OMEPRAZOLE AND AMOXICILLIN

The least squares estimates with 95% confidence intervals for the treatment effect with respect to $AUC_{(0-t)}$ and C_{max} of omeprazole and amoxicillin alone or in combination are shown in Table 3 and 5. The least squares estimates of the treatment ratios with respect to $AUC_{(0-t)}$ and C_{max} of omeprazole and amoxicillin are shown in Table 4 and 6. No significant period or sequence effects were found for $AUC_{(0-t)}$ and C_{max} for either omeprazole ($p=0.31, 0.36$) or amoxicillin ($p=0.25, 0.75$).

OMEPRAZOLE

The least squares estimates with 95% confidence intervals for the treatment effect with respect to omeprazole $AUC_{(0-t)}$ (nmol*h/L) and C_{max} (nmol/L) of omeprazole are shown in Table 3. The confidence interval for the mean ratio with respect to $AUC_{(0-t)}$ of omeprazole is within the limits [0.8, 1.25] for bioequivalence (Table 4). Concerning C_{max} , the confidence interval for the treatment ratio is not included in and is not within the limits for bioequivalence (Table 4).

AMOXICILLIN

Least squares estimates with 95% confidence intervals for amoxicillin $AUC_{(0-t)}$ and C_{max} of amoxicillin are shown in Table 5. The 90% confidence intervals for the mean ratio with respect to $AUC_{(0-t)}$ and C_{max} of amoxicillin are within the limits [0.8, 1.25] for bioequivalence respectively. (Table 6).

PHARMACODYNAMIC EVALUATION

No correlation was found between pHmed and $AUC_{(0-t)}$ of amoxicillin when administered in combination with omeprazole (Correlation 0.1414, p-value 0.5002).

DISCUSSION: Omeprazole in high doses did not influence the bioavailability of amoxicillin. The bioavailability in terms of AUC and C_{max} was equivalent when healthy volunteers were given amoxicillin alone or amoxicillin in combination with omeprazole. The statistical analysis was based on the estimates of the ratios between amoxicillin and amoxicillin combined with omeprazole with respect to AUC and C_{max} and 90% confidence intervals. Amoxicillin alone was bioequivalent with amoxicillin in combination with omeprazole, since the 90% confidence intervals for both AUC and C_{max} were within the limits [0.8, 1.25] established for bioequivalence. In terms of AUC omeprazole alone was bioequivalent with omeprazole in combination with amoxicillin, since the 90% confidence intervals were within the bioequivalence limits; bioequivalence could not be shown for C_{max} . However, for omeprazole AUC is considered to be

the important variable in determining the acid secretion control. It is unclear, whether the lower omeprazole AUC after the evening dose was due to a reduced absorption, or to an increased metabolism of the drug. As the stomach was hypoacidic at the morning and the evening administration, it is unlikely, that the lower serum concentrations at night were caused by acid degradation of omeprazole.

Irrespective of treatment group, 26 AEs were reported for a total of 13 subjects. Four AEs were reported for three subjects given omeprazole, six AEs were reported for four subjects given amoxicillin and 16 AEs were reported for six subjects given the combination omeprazole and amoxicillin.

CONCLUSIONS: Data from the study showed that no pharmacokinetic interaction between omeprazole and amoxicillin because both drugs were bioequivalent when administered in combination as compared to administration alone. Also, the intragastric pH does not influence the bioavailability of amoxicillin. However, because assay validation and quality control data is not available, the study is not acceptable.

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Table 3 Least squares estimates with 95% confidence intervals for the treatment effect with respect to $AUC_{0-\infty}$ and C_{max} of omeprazole.

Treatment:	Variable	Estimate	Confidence interval	
			Lower	Upper
omeprazole (single):	$AUC_{0-\infty}$	15733	14690	23939
omeprazole (combi):	$AUC_{0-\infty}$	19244	15076	24567
omeprazole (single):	C_{max}	4875	3922	6061
omeprazole (combi):	C_{max}	4485	3607	5577

Table 5 Least squares estimates with 95% confidence intervals for amoxicillin $AUC_{0-\infty}$ (nmol^h/L) and C_{max} (nmol/L).

Treatment:	Variable	Estimate	Confidence interval	
			Lower	Upper
amox. (single):	$AUC_{0-\infty}$	86904	78425	96300
amox. (combi):	$AUC_{0-\infty}$	90040	81572	99629
amox. (single):	C_{max}	18715	17071	20518
amox. (combi):	C_{max}	18082	16514	19796

Table 4 Least squares estimates of the treatment ratios with respect to $AUC_{0-\infty}$ and C_{max} of omeprazole.

Treatment:	Variable	Estimate	90% confidence interval		P-value
			Lower	Upper	
ome. (single)/ ome. (combi)	$AUC_{0-\infty}$	0.9744	0.8401	1.1303	0.7678
ome. (single)/ ome. (combi)	C_{max}	1.0869	0.9046	1.3046	0.4448

Table 6 Least squares estimates of the treatment ratios with respect to $AUC_{0-\infty}$ and C_{max} of amoxicillin.

Treatment	Variable	Estimate	90% confidence interval		P-value
			Lower	Upper	
amox. (single)/ amox. (combi)	$AUC_{0-\infty}$	0.96517	0.8672	1.0742	0.5756
amox. (single)/ amox. (combi)	C_{max}	1.0350	0.9417	1.1375	0.5385

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TITLE: Bioavailability of Antibiotics after Single Oral Administration of Amoxicillin, Erythromycin, Phenoxymethylpenicillin and Roxithromycin before and after Treatment with Omeprazole (Study No. I-1221; Vol. 4; pp.006-001-227 to 006-001-280)

INVESTIGATOR: Robert Bergstrand, MD, Ph.D., Astra Hässle AB, S-413 83 Mölndal, Sweden.

OBJECTIVES:

1. To assess the plasma concentration of amoxicillin, erythromycin, phenoxymethylpenicillin or roxithromycin after single oral administrations of the drugs.
2. To evaluate the influence of the intragastric pH on the stability of the antibiotics by administering the antibiotics with and without concomitant omeprazole treatment.

SUBJECTS: Eight healthy male subjects were included.

STUDY DESIGN: The study was conducted as a six week single blind, randomized trial consisting of 8 investigational periods in which 4 antibiotics: amoxicillin, erythromycin base, phenoxymethylpenicillin and roxithromycin were given orally during placebo and concomitant treatment of omeprazole 40 mg twice daily. The study was performed as a two way cross over study with respect to omeprazole i.e. half of the subjects received omeprazole and half received placebo the first week. Within each period, the antibiotics as well as the omeprazole was administered in a Latin square design, balanced for residual effects. Each investigational period involving roxithromycin was followed by a wash-out period of at least six days and a minimum of two days passed between the three other periods involving the other antibiotics. Blood samples were collected over 12-hour period.

FORMULATIONS:

Omeprazole (Losec®, Astra AB, Södertälje) 20 mg each, was given orally as enteric coated granules, dispensed in hard gelatin capsules. Batch number: H431-13-5-3.

Placebo capsules, identical in appearance to the omeprazole capsules, were used. Batch number: H459-6-3-2.

Amoxicillin (Imacillin®, Astra AB, Södertälje) 750 mg each, was given orally as tablets. Batch number: H783-3-1-1.

Erythromycin Base (Astra AB, Södertälje) 250 mg each, was given orally as uncoated granules dispensed in hard gelatine capsules. Batch number: H 1030-2-1-1.

Phenoxymethylpenicillin (Kåvepenin®, Astra AB, Södertälje) 1 g each, was given orally as tablets. Batch number: H 1042-1-1-1.

Roxithromycin (Surlid®, Roussel) 150 mg each, was given orally as tablets. Batch number: H 1032-1-1-1.

The omeprazole/placebo capsules were packed in blister packs, one for each period and subject, by Astra Hässle AB, Mölndal, Sweden. The amoxicillin, erythromycin and phenoxymethylpenicillin were delivered from Astra AB, Södertälje, Sweden. Roxithromycin was purchased from the pharmacy (Apoteksbolaget, Göteborg, Sweden).

SAMPLE COLLECTION:

Blood samples (5 mL) for determination of antibiotics in plasma were collected in heparinized tubes. In each of the experiments blood samples were drawn prior to and at 30 minutes and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after drug intake, with the exception of the experiment when phenoxymethylpenicillin was administered the blood samples were collected up to 8 hours due to its shorter half-life.

ANALYTICAL METHODS: The plasma concentrations of the amoxicillin, erythromycin and roxithromycin were determined by means of techniques at Bioanalytical Chemistry, Astra Hässle AB, Mölndal, Sweden respectively).

The Plasma concentration of phenoxymethylpenicillin was determined by a microbiological technique based on the cylinder plate method with *Micrococcus luteus* as test organism at Infection & Immunology, Preclinical R&D, Astra Arcus AB, Södertälje, Sweden.

PHARMACOKINETIC/DATA ANALYSIS:

The bioavailability was calculated as the area under the plasma concentration time curve (AUC) from 0-8 hours after administration of phenoxymethylpenicillin and from 0-12 hours after administration of the other antibiotics by the trapezoidal method. T_{max} and C_{max} were also assessed. An Analysis of Variance (ANOVA) was performed on the log-transformed values of AUC and C_{max} calculated from plasma concentration of amoxicillin, phenoxymethylpenicillin and roxithromycin. The model included effects for subject(sequence), sequence, treatment and period. Separate analyses were made for each penicillin.

The least squares estimate (the estimate that minimises the residual) were calculated for both omeprazole and placebo separately and also for the ratio of omeprazole and placebo. 95% confidence intervals were calculated as the least squares estimate \pm the t-quantile multiplied by the standard error of the estimate. In a corresponding way 95% confidence intervals for the ratio were calculated.

Non-parametric statistical methods (Wilcoxon's rank-sum test) were used for analyzing AUC and C_{max} calculated from plasma concentration of erythromycin, since the variation between the omeprazole and placebo period differed significantly.

If the p-value for the treatment effect, with respect to either AUC or C_{max} in the ANOVA or Wilcoxon's rank-sum test was lower than 0.05, The conclusion is a significant difference between omeprazole and placebo.

The statistical analysis of T_{max} was made in a similar way using non-parametric statistical methods (Wilcoxon's rank-sum test).

RESULTS: Eight healthy Caucasian male subjects entered and completed the study. The mean demographic data are presented in Table 1.

The plasma concentrations after single oral administrations of four antibiotics (amoxicillin, erythromycin, phenoxymethylpenicillin and roxithromycin) were assessed during placebo and concomitant treatment with omeprazole 40 mg twice daily for three weeks, respectively. From the plasma profiles the AUC, C_{max} and T_{max} values were calculated for each of the antibiotics.

Tables 2 shows the individual and the descriptive statistics of the pharmacokinetic parameters for the eight subjects and the two study periods, respectively. The estimated means and 95% confidence intervals for AUC and C_{max} are shown in Tables 3. Estimate of the ratios of the mean treatment effects of AUC and C_{max} , respectively, and 95% confidence intervals for the ratio of the mean treatment effects are presented in Tables 10 and 11.

The mean plasma concentrations of amoxicillin versus time profile during placebo and concomitant treatment with omeprazole are depicted in Figures 1.

DISCUSSION: There was no indication of an increase of the bioavailability when subjects were given amoxicillin during concomitant treatment with omeprazole, which proves that amoxicillin is more acid stable than the other antibiotics used in this study, and relatively unaffected when the pH of the stomach is changed.

Irrespective of the treatment group 23 adverse events were reported for a total of 8 subjects. Three adverse events were reported for two subjects given omeprazole 40 mg b.i.d. and eight adverse events were reported for four subjects given omeprazole 40 mg b.i.d. plus antibiotics. Six adverse events were reported for three subjects given placebo and six adverse events were reported for three subjects given placebo plus antibiotics.

CONCLUSION: The administration of a single oral dose of amoxicillin after pretreatment with omeprazole did not demonstrate an increase of the bioavailability. However, because assay validation and quality control data is not available, the study is not acceptable.

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Table 1. Mean demographic data (n=8)

	Age (years)	Weight (kg)	Height (cm)
Mean	26	79.6	181.4
SD	2.8	5.7	4.7
Range			

Table 2. Individual values and descriptive statistics for AUC, C_{max} and t_{max} after a single oral dose of amoxicillin 750 mg given during placebo and omeprazole (Ome) administration.

Subject No.	AUC (μmol·h/L)		C _{max} (μmol/L)		t _{max} (h)	
	Placebo	Ome	Placebo	Ome	Placebo	Ome
1						
2						
3						
4						
5						
6						
7						
8						
Mean	119.2	114.0	34.99	30.62	1.75	1.86
SD	21.91	24.50	8.50	6.40	0.46	0.58
Median	118.8	111.4	32.70	29.90	1.75	1.75
Min						
Max						
Geomean	116.9	111.2	33.90	30.11	1.69	1.79

Table 3. Estimated means for AUC and C_{max} after a single oral dose of amoxicillin 750 mg given during placebo and omeprazole administration.

Treatment	AUC (μmol·h/L)			C _{max} (μmol/L)		
	Estimated mean	95% CI lower	95% CI upper	Estimated mean	95% CI lower	95% CI upper
Omeprazole	111.6	106.2	117.4	30.04	26.21	34.44
Placebo	117.4	111.7	123.4	34.17	29.81	39.16

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Table 10. Estimated mean ratios and confidence intervals with an over-all 95% confidence level, for AUC after a single oral dose of amoxicillin 750 mg, erythromycin base 500 mg, phenoxymethylpenicillin 1 g and roxithromycin 150 mg, respectively, given during placebo (Pla) and omeprazole (Ome) administration.

Treatment	Ratio	Estimated mean	95% CI lower	95% CI upper	P-value	Significant
Amoxicillin	Ome/Pla	0.95	0.89	1.02	0.1316	
Erythromycin a)	Ome/Pla	11.43	7.84	15.02	0.0304	*
($\mu\text{mol}\cdot\text{h}/\text{L}$)						
Phenoxymethylpenicillin	Ome/Pla	1.03	0.89	1.19	0.6824	
Roxithromycin	Ome/Pla	3.26	1.62	6.58	0.0062	*

a) Wilcoxon's Rank-Sum test was used in order to detect a significant difference between the treatment effects with respect to AUC and C_{max} of erythromycin.

Table 11. Estimated mean ratios and confidence intervals with an over-all 95% confidence level, for C_{max} after a single oral dose of amoxicillin 750 mg, erythromycin base 500 mg, phenoxymethylpenicillin 1 g and roxithromycin 150 mg, respectively, given during placebo (Pla) and omeprazole (Ome) administration.

Treatment	Ratio	Estimated mean	95% CI lower	95% CI upper	P-value	Significant
Amoxicillin	Ome/Pla	0.88	0.72	1.07	0.1542	
Erythromycin a)	Ome/Pla	4.78	2.78	6.78	0.0304	*
($\mu\text{mol}\cdot\text{h}/\text{L}$)						
Phenoxymethylpenicillin	Ome/Pla	1.34	1.10	1.64	0.0116	*
Roxithromycin	Ome/Pla	4.17	2.06	8.44	0.0026	*

a) Wilcoxon's Rank-Sum test was used in order to detect a significant difference between the treatment effects with respect to AUC and C_{max} of erythromycin.

Mean plasma conc. of amoxicillin ($\mu\text{mol}/\text{L}$)

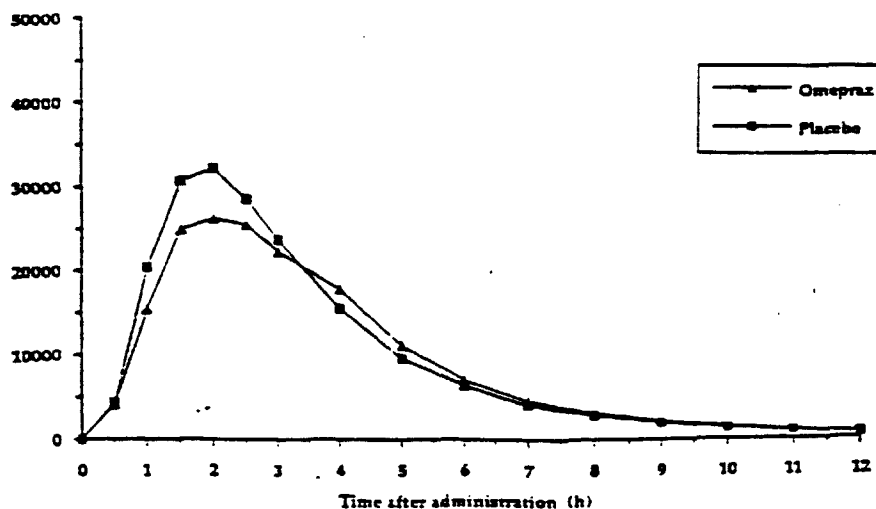


Figure 1. Mean amoxicillin plasma concentrations during placebo and concomitant treatment with omeprazole (n=8).

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TITLE: Gastrointestinal transit of amoxicillin modified-release tablets and a placebo tablet, including pharmacokinetic assessment of amoxicillin (Protocol No. I-1214; Vol. 5; pp. 006-002-001 to 006-002-253)

INVESTIGATOR:

OBJECTIVES: The study was performed in order to study:

1. The transit time of the amoxicillin MR tablet in different parts of the gastrointestinal tract during fasting and non-fasting conditions.
2. The influence of tablet shape on the gastric residence time.
3. The disintegration time of the amoxicillin MR tablets.
4. The absorption of amoxicillin as reflected by plasma concentrations of amoxicillin given as a MR or IR tablet.

SUBJECTS: Six Caucasian healthy male subjects were recruited. All subjects completed the study as per protocol and were analyzed accordingly.

STUDY DESIGN: The study was conducted as an open, randomized, cross-over trial consisting of three study periods. The subjects were initially taken omeprazole 40 mg once daily for five days in order to reach steady state level in terms of inhibition of acid secretion. During continuous omeprazole treatment, three experiments were performed in which two labelled amoxicillin MR tablets 375 mg and a non-disintegrating placebo tablet were administered during either fasting condition or together with a light or heavy breakfast.

measurements were performed and blood samples were taken repeatedly after administration in each experiment. In an additional experiment commercially available amoxicillin 750 mg tablet (Imacillin®) was given with a light breakfast to obtain plasma profiles for this formulation that enables comparison to the modified-release tablet with respect to relative bioavailability.

Between the four experiments a wash-out period of at least two days was necessary for the elimination of amoxicillin. The contents of the standardized meals were as follows:

1. Light breakfast: (approximately 1500 kJ)
2 pieces of bread, 10 g diet margarin, 40 g cheese and 150 mL orange juice.
2. Heavy breakfast: (approximately 3000 kJ)
3 pieces of bread, 20 g diet margarin, 40 g cheese, 30 g cereals, 200 g yogurt and 300 mL orange juice.

All subjects took one omeprazole 40 mg capsule each morning before breakfast, a single dose of two amoxicillin modified-release tablets 375 mg and one non-disintegrating placebo tablet were administered together with omeprazole. In an additional experiment Imacillin® was given during intake of a light breakfast.

FORMULATIONS: 1. Amoxicillin modified-release tablets 375 mg, labelled with (amoxicillin MR). 2. Non-disintegrating placebo tablet, labelled with (placebo). Both were manufactured by Astra Hässle AB, Mölndal, Sweden. 3. Imacillin® (amoxicillin IR) was given orally. Each tablet contains 2x350 mg of amoxicillin. Amoxicillin IR was manufactured by Astra AB, Sweden. 4. Losec® (omeprazole) was given orally as granules dispersed in hard gelatin capsules. Each capsule contains 40 mg of omeprazole. Omeprazole was manufactured by Astra AB, Sweden.

SAMPLE COLLECTION: Blood sampling (5 mL) for the determination of amoxicillin in plasma were collected at -5, 0, 15, 30, 45 mins, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 24 hrs.

ANALYTICAL METHODS: The plasma samples were analyzed for amoxicillin at Bioanalytical Chemistry, Astra Hässle AB.

PHARMACOKINETIC/DATA ANALYSIS: Plasma concentration time curves of amoxicillin were assessed for each individual, and C_{max} , T_{max} , AUC were calculated. The log-transformed and kinetic variables were analyzed using an ANOVA with factors for subjects, period, treatment and carry over effects. The mean square error from the ANOVA was used to calculate 95% confidence intervals for each of the food intake conditions as well as for their ratios and p-values from the corresponding ANOVA were also given.

RESULTS: The tablets were emptied from the stomach within 1.0 h (amoxicillin MR) and 0.6 h (placebo) in all subjects after administration under fasting conditions. The estimated mean gastric residence time after administration of a light breakfast was 4.3 h (amoxicillin MR) and 3.0 h (placebo). The estimated mean gastric residence time after administration of a heavy breakfast was 4.9 h (amoxicillin MR) and 3.5 h (placebo). The gastric residence time of amoxicillin MR tablets was prolonged by the concomitant intake of breakfast with 4.0 h (light breakfast) and 4.6 h (heavy breakfast). There are significant differences between fasting and heavy breakfast $p < 0.0001$ and also between fasting and light breakfast $p < 0.0001$ with respect to estimated mean gastric residence time. There is no significant difference in gastric residence time between administration of light and heavy breakfast $p > 0.05$.

The estimated means of small intestinal transit time for fasting subjects were 4.7 h (amoxicillin MR) and 5.9 h (placebo). The estimated means of small intestinal transit time after administration of a light breakfast were 4.8 h (amoxicillin MR) and 6.0 h (placebo). After administration of a heavy breakfast the estimated mean small intestinal transit time was 3.4 h (amoxicillin MR) and 4.3 h (placebo). There were no significant differences in small intestinal transit time between any of the three breakfast regimens. The estimated mean colon arrival time of amoxicillin MR was 4.9, 8.5, and 9.1 hours for fasting, light and heavy breakfast, respectively. The mean colon arrival time of placebo tablet was 5.4, 9.4 and 10.0 hours for fasting, light and heavy breakfast, respectively. No evidence of significant differences was found for the estimated mean colon arrival time for amoxicillin MR and placebo independent of breakfast regimens.

There were no indications of totally disintegrated amoxicillin MR tablets during the first 12 hours after intake. Twenty-four hours after intake 25% of the tablets was found as partially disintegrated.

The mean plasma concentrations of amoxicillin MR following administration of three different breakfast regimens and IR following administration of a light breakfast are shown in Figure 2. Individual values and estimated mean values for AUC and C_{max} are shown in Tables 3 and 4, respectively. The plasma profiles of amoxicillin MR and IR were similar in shape when administered during fasting, together with light or heavy breakfast. The AUCs of amoxicillin for MR formulation were similar during fasting, intake of light and heavy breakfast. However, there was a statistical significance (Table 6) between the two different formulations of amoxicillin (MR and IR) for the breakfast regimen evaluated.

CONCLUSION: The study was reviewed. However, because assay validation and quality control data is not available, the study is not acceptable.

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Figure 2. Mean plasma concentration (nmol/l) of amoxicillin following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and amoxicillin IR 2x375 mg with light breakfast.

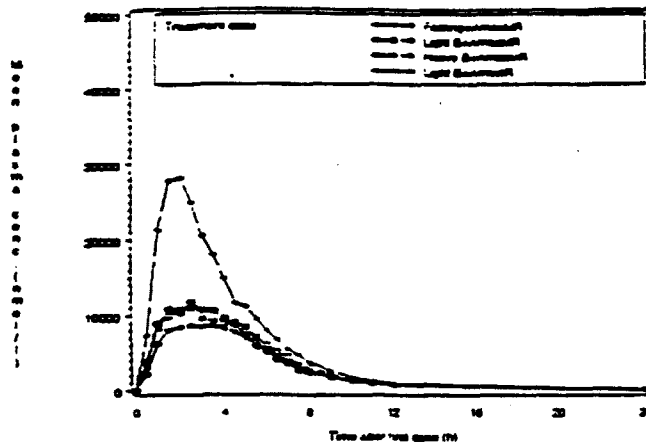


Table 3. shows individual and estimated mean AUC ($\mu\text{mol/l}$) following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and administration of amoxicillin IR 2x375 mg with light breakfast.

Subject no	Amox MR			Amox IR
	F	LB	HB	LB
1				
2				
3				
4				
5				
6				
LSMEAN	68.3	69.2	58.7	124.9
95%CI	58.8-79.4	59.9-80.0	50.5-68.2	105.7-147.6

Table 4. Individual and estimated mean C_{max} ($\mu\text{mol/l}$) following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and administration of amoxicillin IR 2x375 mg with light breakfast.

Subject no.	Amox MR			Amox IR
	F	LB	HB	LB
1				
2				
3				
4				
5				
6				
LSMEAN	13	11.4	8.9	29.7
95%CI	11.3-15.0	9.8-13.1	7.7-10.2	25.4-34.7

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Figure 2. Mean plasma concentration (nmol/l) of amoxicillin following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and amoxicillin IR 2x375 mg with light breakfast.

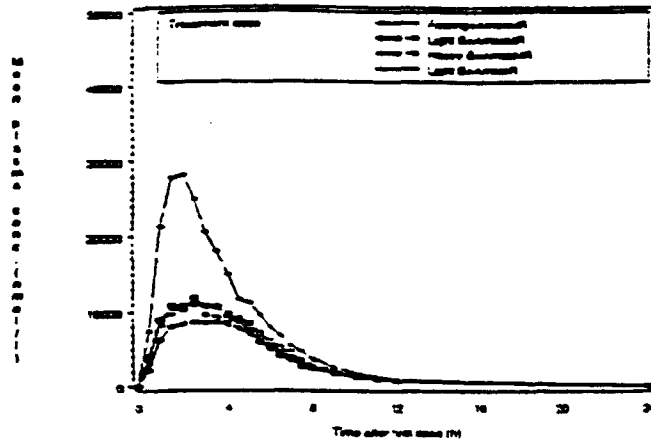


Table 3. shows individual and estimated mean AUC ($\mu\text{mol/l}$) following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and administration of amoxicillin IR 2x375 mg with light breakfast.

Subject no.	Amox MR			Amox IR
	F	LS	HB	LS
1				
2				
3				
4				
5				
6				
LSMEAN	68.3	69.2	58.7	124.9
95%CI	58.3-79.4	59.9-80.0	50.5-68.2	105.7-147.6

Table 4. Individual and estimated mean C_{max} ($\mu\text{mol/l}$) following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and administration of amoxicillin IR 2x375 mg with light breakfast.

Subject no.	Amox MR			Amox IR
	F	LS	HB	LS
1				
2				
3				
4				
5				
6				
LSMEAN	13	11.4	8.9	29.7
95%CI	11.3-15.0	9.8-13.1	7.7-10.2	25.4-34.7

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Table 5. Individual, mean SD and median t_{max} (hours) following administration of amoxicillin MR 2x375 mg with fasting, light and heavy breakfast and administration of amoxicillin IR 2x375 mg with light breakfast.

Subject no.	Amox MR			Amox IR
	F	LB	HB	LB
1				
2				
3				
4				
5				
6				
Mean	2.4	2.2	2.8	2.0
SD	0.8	0.4	0.9	0.8
LSMEAN	2.5	2.2	2.8	1.8

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TITLE: An interaction study between omeprazole, amoxicillin and clarithromycin (SH-OMH-0016). Vol. 3, pp.003-001 to 003-216.

INVESTIGATOR:

OBJECTIVE: To investigate potential pharmacokinetic drug-drug interactions between omeprazole, amoxicillin and clarithromycin after repeated oral administration in healthy subjects.

SUBJECTS: Sixteen healthy male (n=10) and female (n=6) subjects were included.

STUDY DESIGN: The study was an open-label, randomized, four-way, cross-over. The subjects were given omeprazole, 20 mg bid, amoxicillin, 1g bid, or clarithromycin 500 mg bid, for 7 days or the triple combination twice daily also during 7 days.

FORMULATIONS: Omeprazole (Losec®, Astra Hässle AB, 20 mg capsules, batch no. H 0431-14-03-10), amoxicillin (Imacillin®, Smith Klein & Beecham/Astra, 1g tablets, batch no. H 1035-03-03-01), and clarithromycin (Bremon®, Abbott Laboratories, 250 mg tablets, batch no. H 1031-02-01-06).

SAMPLE COLLECTION:

A reference blood sample was collected before the study drug(s) were administered. Further blood samples were taken every 15 minutes up to 2 hours, at 2.5 hours and at 3, 4, 6, 8, 10, and 12 hours post dose on day 7 and on days 5 and 6 in each period. There was a two weeks wash-out period between each treatment period.

ANALYTICAL METHODS:

The concentration of omeprazole was determined at Bioanalytical Chemistry, Astra Hässle AB, using a _____ method with a _____

Clarithromycin and 14-hydroxyclearithromycin were determined at _____ using a _____ method with an _____ Amoxicillin was analyzed at _____

PHARMACOKINETIC/DATA ANALYSIS:

The pharmacokinetic parameters C_{max} , T_{max} , AUC, and $t_{1/2}$ were determined by non-compartmental methods using WinNonlin v. 1.1. A mixed analysis of variance model, with the logarithms of AUC, C_{max} , and $t_{1/2}$, one at a time as the dependent variable, was used. All main effects were tested against the residual error from the ANOVA. The individual log-transformed mean effects were estimated and 95% confidence intervals were constructed.

RESULTS: The mean plasma concentrations of omeprazole on day 7, both following single drug treatment and following the combination treatment, are presented in Figure 2. The mean plasma concentrations of omeprazole are higher after triple drug administration than after single

drug administration over the whole 12 hour measurement period. This is reflected in a two-fold increase in mean AUC and a 68% increase in mean C_{max} (Table 2). The $t_{1/2}$ of omeprazole was also slightly longer (32%) while the T_{max} did not seem to be altered during triple drug administration as compared to administration of omeprazole alone.

The mean plasma concentrations of amoxicillin after triple drug administration is slightly higher (Figure 3) than those obtained after administration of amoxicillin alone. The mean C_{max} and AUC of amoxicillin were higher during triple treatment than during single drug administration (Table 3). The $t_{1/2}$ of amoxicillin could not be determined properly.

The mean plasma concentrations of clarithromycin and of 14-hydroxyclearithromycin are slightly higher during triple drug administration than during administration of clarithromycin alone (Figure 4). The C_{max} and AUC of 14-hydroxyclearithromycin were approximately 30% higher during triple drug treatment than during single drug administration (Table 4). The pharmacokinetic variables of clarithromycin were not statistically significantly different between the two treatments.

SAFETY: 37 AEs were reported for all 16 subjects treated with the triple combination of omeprazole, amoxicillin and clarithromycin. The most common events were diarrhea, headache, taste perversion, flatulence and respiratory infection.

DISCUSSION: Sponsor stated that the increased plasma levels of omeprazole is a result of inhibition of the metabolism of omeprazole caused by clarithromycin treatment. The prolongation of the elimination half life of omeprazole indicates that not only the first pass elimination of omeprazole is decreased but also the systemic clearance. Amoxicillin slight increase in C_{max} and AUC may not be clinically significant. The sponsor further stated that the effects seen during the triple combination on the plasma levels of omeprazole and 14-hydroxyclearithromycin are judged to be caused by a mutual interaction between omeprazole and clarithromycin with no influence of amoxicillin.

CONCLUSIONS: The sponsor concluded that the metabolic inhibition by clarithromycin on the metabolism of omeprazole is not likely to be of clinical importance. And, the slightly increased plasma levels of 14-hydroxyclearithromycin and of amoxicillin observed during combined treatment is probably of no major clinical significance. Therefore, treatment with a combination of omeprazole, clarithromycin, and amoxicillin during a seven days is safe and well tolerated. However, because assay validation and quality control data is not available, the study is not acceptable.

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Table 3. Pharmacokinetic variables (geometric mean values with 95% confidence intervals (CI) for C_{max} and AUC, median and range for t_{max}) of amoxicillin following repeated administration of 1 g twice daily either alone (A), or as triple treatment in combination with omeprazole and clarithromycin (OCA).

	C_{max} (μM)	t_{max} (h)	AUC (μM·h)
Amoxicillin alone (A)	28.0	1.53	81.1
95% CI/range	23.7-33.1	1.00-3.00	71.5-92.1
Amoxicillin in triple (OCA)	32.4	1.75	89.6
95% CI/range	27.5-38.3	1.00-1.50	79.0-101.7
Ratio OCA/A	1.16	1.07	1.10
95% CI	1.03-1.30	ND	1.00-1.22

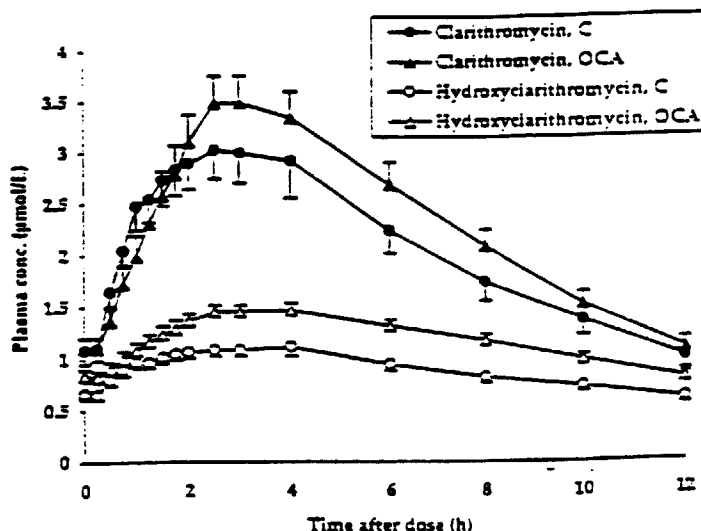


Figure 4. The mean (SEM) plasma concentrations of clarithromycin and its 14-hydroxy-metabolite on day 7, both following administration of clarithromycin, 500 mg bid, alone (C) and in combination (OCA) with omeprazole (20 mg bid) and amoxicillin (1 g bid) (n=16).

Table 4. Pharmacokinetic variables (geometric mean values with 95% confidence intervals (CI) for C_{max} , AUC and $t_{1/2}$, median and range for t_{max}) of clarithromycin and 14-hydroxyclearithromycin following repeated administration of clarithromycin 500 mg twice daily either alone (C) or as triple treatment in combination with omeprazole and amoxicillin (OCA).

	C_{max} (μM)	t_{max} (h)	AUC (μM·h)	$t_{1/2}$ (h)
Clarithromycin				
Clarithromycin alone (C)	3.06	2.50	23.2	5.13
95% CI/range	2.53-3.70	1.00-6.00	19.2-28.0	4.29-6.14
Clarithromycin triple (OCA)	3.42	2.50	26.4	4.29
95% CI/range	2.83-4.14	1.50-3.00	21.9-31.9	3.59-5.13
Ratio OCA/C	1.12	1.0	1.14	0.84
95% CI	0.89-1.40	ND	0.95-1.36	0.65-1.08
14-Hydroxyclearithromycin				
Clarithromycin alone (C)	1.13	2.50	10.4	9.28
95% CI/range	0.98-1.29	0.75-6.00	9.18-11.8	7.53-11.29
Clarithromycin triple (OCA)	1.47	3.00	14.0	7.31
95% CI/range	1.28-1.68	1.50-4.00	12.4-15.8	6.01-8.99
Ratio OCA/C	1.31	1.2	1.34	0.79
95% CI	1.08-1.58	ND	1.15-1.57	0.60-1.04

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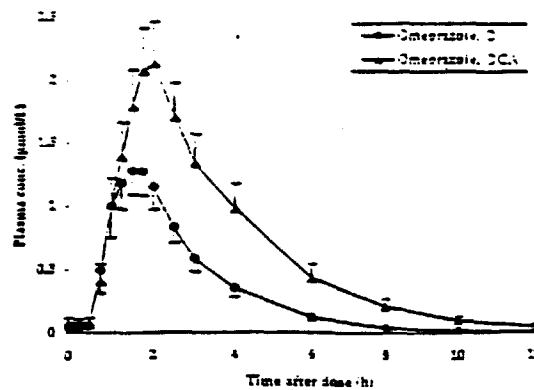


Figure 2. The mean (SEM) plasma concentrations of omeprazole on day 7, both following administration of omeprazole, 20 mg bid, alone (C) and in Table 1. Pharmacokinetic variables (geometric mean values with 95% confidence intervals (CI) for C_{max} , AUC and $t_{1/2}$, median and range for t_{max}) of omeprazole following repeated administration of 20 mg twice daily either alone (C) or as triple treatment in combination with amoxicillin and clarithromycin (CCA).

	C_{max} (µM)	t_{max} (h)	AUC (µM·h)	$t_{1/2}$ (h)
Omeprazole alone (C)	2.45	1.50	2.22	0.91
95% CI, range	1.10-4.91	0.73-2.31	1.50-3.94	0.73-1.13
Omeprazole in triple (CCA)	2.43	1.53	3.53	1.21
95% CI, range	1.34-3.51	1.00-3.00	3.35-4.23	0.99-1.47
Ratio CCA/C	1.45	1.09	2.10	1.33
95% CI	1.31-2.15	ND	1.35-2.78	1.13-1.53

µM=µmol/L

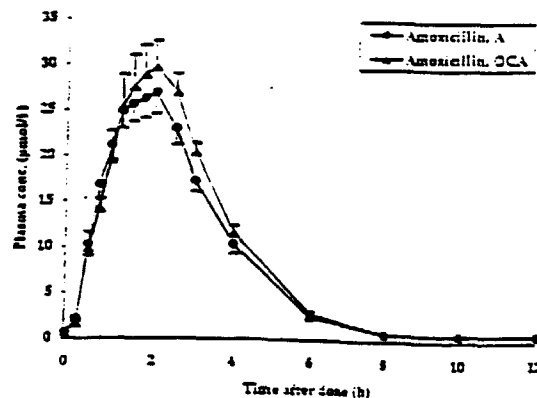


Figure 3. The mean (SEM) plasma concentrations of amoxicillin on day 7, both following administration of amoxicillin, 1 g bid, alone (A) and in combination (CCA) with omeprazole (20 mg bid) and clarithromycin (500 mg bid) (n=16).

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